16. Ultratrace Minerals[1]

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Ultratrace minerals are those elements with estimated dietary requirements usually less than 1 μg/g and often less than 50 ng/g of diet for laboratory animals (1). For humans, the term often is used for mineral elements with established, estimated, or suspected requirements below 1 mg/day, often expressed in micrograms per day. At least 18 elements could be considered ultratrace minerals: aluminum, arsenic, boron, bromine, cadmium, chromium, fluoride, germanium, iodine, lead, lithium, molybdenum, nickel, rubidium, selenium, silicon, tin, and vanadium. Two additional elements, cobalt and manganese, perhaps belong in the ultratrace category also. Although cobalt is required in ultratrace amounts, it has to be in the form of vitamin B_{12}; thus, it is usually discussed as a vitamin and is not considered here. An estimated safe and adequate daily dietary intake (ESADDI) for manganese of 2.5 to 5.0 mg/day has been established for adults (2); however, recent studies with humans suggest that the actual requirement may be near 1.0 mg/day. Even if it is above 1.0

[1] U.S. Department of Agriculture, Agriculture Research Service, Northern Plains Area. An equal opportunity/affirmative action employer and all agency services are available without discrimination.

mg/day, knowledge about the practical importance or beneficial actions of manganese is in a state similar to that for most of the ultratrace minerals; therefore it belongs in the discussion of the ultratrace minerals.

The quality of the experimental evidence for nutritional essentiality varies widely for the ultratrace elements. Evidence for the essentiality of the four elements iodine, manganese, molybdenum, and selenium is substantial and noncontroversial; specific biochemical functions have been defined for these elements. The nutritional importance of iodine and selenium are such that separate chapters have been devoted to them in this treatise. Manganese and molybdenum, however, are given less nutritional attention, apparently because deficiencies of these elements have only been unequivocally identified in a few individuals nourished by total parenteral nutrition (TPN) or with genetic defects causing metabolic disturbances involving these elements. Specific biochemical functions have not been defined for the other 15 elements; thus, their essentiality is based on circumstantial evidence, which most often is that dietary deprivation in some animal model results in a suboptimal biologic function that is prevented or reversed by an intake of physiologic amounts of the element in question. Often the circumstantial evidence includes biochemical actions suggesting a biologic role or beneficial actions in humans. The circumstantial evidence for essentiality is substantial for arsenic, boron, chromium, nickel, silicon, and vanadium; thus, except for chromium (discussed in Chapter 15), they are discussed in detail here. The evidence for essentiality of the other elements is generally limited to a few gross observations in one or two species by one or two research groups. Because it was judged premature to discuss these elements in detail here, they are only briefly mentioned at the end of the chapter. However, fluoride, which has a well-known beneficial pharmacologic property (anticariogenic), is discussed in detail.

ARSENIC

Historical Overview

For about 1100 years, through the 19th century, arsenic reigned as the king of poisons because some arsenic compounds were found to be convenient, scentless, and tasteless instruments for homicide. Although arsenic was considered synonymous with poison, by 1937, the pharmacologic actions of 8000 arsenicals had been recorded. Arsenicals were used at various times for the treatment of anorexia and other nutritional disturbances, syphilis, neuralgia, rheumatism, asthma, chorea, malaria, tuberculosis, diabetes, various skin diseases, and numerous hematologic abnormalities (3). The use of arsenicals for these disorders has either fallen into disrepute or been replaced by more effective alternatives. Although attempts to produce a nutritional arsenic deficiency first occurred in the 1930s, the first substantial evidence for arsenic essentiality appeared in 1975 and 1976 (4).

Chemistry

Both trivalent and pentavalent arsenic exists in biologic material. The most biochemically important organic arsenic compounds are those that contain methyl groups. Methylation of inorganic oxyarsenic anions occurs in organisms ranging from microbial to mammalian. The methylated end-products include arsenocholine, arsenobetaine, dimethylarsinic acid, and methylarsonic acid.

Other arsenic compounds of interest may be biologic molecules in which phosphate is replaced by arsenate. The relatively unstable nature of arsenyl esters is apparently why there is no direct evidence for the existence of compounds such as glucose-6-arsenate and adenosine diphosphate-arsenate. Nonetheless, an arsenate ester might be the form of arsenic that performs an essential function.

A comprehensive review of arsenic chemistry and biochemistry has been published (5).

Metabolism

Absorption of inorganic arsenic from the gastrointestinal tract correlates well with the solubility of the compound ingested (6). In humans and most laboratory animals, more than 90% of inorganic arsenate and arsenite fed in a water solution is absorbed (6). About 60 to 75% of inorganic arsenic ingested with food is absorbed (7). On the other hand, only 20 to 30% of arsenic in arsenic trioxide or lead arsenate, which are only slightly soluble in water, is absorbed by hamsters, rats, and rabbits.

The form of organic arsenic also determines how well it is absorbed. For example, when orally dosed, more than 90% of arsenobetaine was recovered in the urine of hamsters (8); 70 to 80% of arsenocholine was recovered in the urine of mice, rats, and rabbits (9); and 45% of dimethylarsinic acid was recovered in the urine of hamsters (10). In contrast, arsenosugars as found in seaweed are poorly absorbed from the gastrointestinal tract (10). They must be metabolized to another form before the arsenic can be absorbed.

Contrary to what once was believed, arsenate and phosphate, despite structural similarities, do not share a common transport pathway in the duodenum (12). The absorption of arsenate can be separated into two components. First, arsenate becomes sequestered primarily in or on the mucosal tissue. Eventually, the sites of sequestration become filled, with concomitant movement of arsenate into the body. The absorption of arsenate apparently involves a simple movement down a concentration gradient. In rats, some forms of organic arsenic are absorbed at rates directly proportional to their intestinal concentration over a 100-fold range. This finding suggests that organic arsenicals are absorbed mainly by simple diffusion through lipoid regions of the intestinal boundary.

Once absorbed, inorganic arsenic is transferred to the liver, where it is methylated with S-adenosylmethionine as the methyl donor (13). Before arsenate is methylated, it is

reduced to arsenite in a reduction facilitated by glutathione (13). Arsenite methyltransferase is the enzyme that methylates arsenite. Methylation of the monomethylarsenic acid by monomethylarsenic acid methyltransferase, yields dimethylarsinic acid, the major form of arsenic in urine (14). The methylation of arsenic can be modified by changing the glutathione, methionine, and choline status of the animal (13).

The fate of absorbed organic arsenic depends on its form. For example, arsenobetaine passes through the body into the urine without biotransformation. Some orally ingested arsenocholine appears in the urine, and some is incorporated into body phospholipids in a manner similar to choline; however, most is transformed to arsenobetaine before being excreted in the urine.

Excretion of ingested arsenic is rapid, principally in urine. In some species, significant amounts of arsenic are excreted in the bile in association with glutathione (13). The usual proportions of the forms of arsenic in human urine is about 25% inorganic arsenic, 20% monomethylarsenic acid, and 55% dimethylarsinic acid (7). The proportions are quite different, however, with the consumption of organic arsenic. For example, an analysis of urine from 102 Japanese students who consumed luxuriant amounts of organic arsenic in seafood revealed 9.4% inorganic arsenic, 3.0% monomethylarsenic acid, 28.9% dimethylarsinic acid, and 58.2% trimethylated arsenic compound (15).

Functions and Mode of Action

The metabolic function of arsenic is not clearly defined. Recent findings suggest that arsenic has a biochemical role that affects the metabolism of the amino acid methionine or is involved in labile methyl-group metabolism. For example, arsenic deprivation has been found to slightly increase liver *S*-adenosylhomocysteine (SAH) and decrease liver *S*-adenosylmethionine (SAM) concentrations, thus resulting in a decreased SAM:SAH ratio (16); SAM and SAH are involved in methyl transfer. Also, arsenic deprivation depressed the concentration of the methionine metabolite taurine in plasma of hamsters and rats (17).

Arsenic possibly has a role in some enzymatic reaction. However, although arsenic has been found to activate some enzymes, this probably occurs because arsenate can act as a substitute for phosphate. Arsenic as arsenite inhibits many enzymes by reacting with key sulfhydryl groups.

Another possible role for arsenic is in the regulation of gene expression. Arsenite can induce the isolated cell production of certain proteins known as heat shock or stress proteins. Arsenite apparently has an effect at the transcriptional level, which may involve changes in the methylation of core histones (18). Recently, it has been shown that arsenic increases the methylation of the *p53* promoter, or DNA, in human lung cells (19). Also, arsenic enhances DNA synthesis in unsensitized human lymphocytes and in those stimulated by phytohemagglutinin (20).

Deficiency Signs

Arsenic deprivation has been induced in chickens, hamsters, goats, miniature pigs, and rats (4, 16, 17, 21). In the goat, miniature pig, and rat, the most consistent signs of arsenic deprivation were depressed growth and abnormal reproduction characterized by impaired fertility and increased perinatal mortality. Other notable signs of deprivation in goats were depressed serum triglyceride concentrations and death during lactation. Myocardial damage also occurred in lactating goats. The organelle of the myocardium most markedly affected was the mitochondrion at the membrane level. In advanced stages of deficiency, the membrane actually ruptured. Other reported signs of arsenic deprivation include changes in mineral concentrations in various organs. However, listing all signs may be misleading because the nature and severity of the signs of arsenic deprivation are affected by other factors. For example, female rats fed a diet conducive to kidney calcification have more severe calcification when dietary arsenic is low; kidney iron was also elevated (16). Male rats fed the same diet do not show these changes. Other factors that can affect the response to arsenic deprivation include variations in the dietary concentrations of zinc, arginine, choline, methionine, taurine, and guanidoacetic acid. Generally, the signs of arsenic deprivation can be changed and enhanced by nutritional stressors that affect sulfur amino acid or labile methyl-group metabolism.

Toxicology

Because mechanisms exist for homeostatic regulation of arsenic, its toxicity through oral intake is relatively low; it is actually less toxic than selenium, an ultratrace element with well-established nutritional value. Toxic quantities of inorganic arsenic generally are reported in milligrams. For example, reported estimated fatal acute doses of arsenic for humans range from 0.9 to 1.50 mmol (70–300 mg) or about 13 to 53 μmol (1.0–4.0 mg) As/kg body weight (22). These doses suggest that the human is more sensitive to the acute lethal effects of arsenic than are experimental animals. The ratio of the toxic to nutritional dose for rats apparently is near 1250. Some forms of organic arsenic are virtually nontoxic; a 56 mmol (10 g)/kg body weight dose of arsenobetaine depressed spontaneous motility and respiration in male mice, but these symptoms disappeared within 1 hour (23).

Briefly, the signs of subacute and chronic high exposure of arsenic in humans include the development of dermatoses of various types (hyperpigmentation, hyperkeratosis, desquamation, and hair loss); hematopoietic depression; liver damage characterized by jaundice, portal cirrhosis, and ascites; sensory disturbances; peripheral neuritis; anorexia; and loss of weight (24). A reference dose (RfD, lifetime exposure that is unlikely to cause

adverse health effects) of 4.0 nmol (0.3 μg)/kg body weight/day has been suggested for arsenic (25).

Results of numerous epidemiologic studies suggest an association between chronic arsenic overexposure and the incidence of some forms of cancer, particularly skin cancer; however, the role of arsenic in carcinogenesis remains controversial. Arsenic does not seem to act as a primary carcinogen and is either an inactive or extremely weak mitogen.

Dietary Considerations

Only data from animal studies are available for estimating the possible arsenic requirement of humans. An arsenic requirement between 83 and 167 nmol (6.25 and 12.5 μg)/4.18 MJ (1000 kcal) was suggested for growing chicks and rats (26). Thus, a possible arsenic requirement for humans eating 8.37 MJ (2000 kcal) would be about 160 to 200 nmol (12–25 μg) daily. Reports from various parts of the world indicate that the average daily intake of arsenic is in the range of 160 to 800 nmol (12–60 μg) (26, 27). In the United States, the individual mean total arsenic intake from all food, excluding shellfish, has been estimated to be 400 nmol (30 μg)/day (27). Fish, grain, and cereal products contribute the most arsenic to the diet. Clarification of the need for arsenic for optimal health and performance is needed so that a safe and adequate intake of the element can be established.

Clinical Considerations

Until more is known about the biochemical and physiologic functions of arsenic, it is inappropriate to associate specific disorders with deficient arsenic nutriture. However, it has been suggested that arsenic could play an essential role in humans because injuries of the central nervous system, vascular diseases, and cancer were correlated with markedly decreased serum arsenic concentrations (28). Perhaps the most important consideration at present is recognizing the likelihood that arsenic is essential for humans. The belief that any form or amount of arsenic is unnecessary, toxic, or carcinogenic is unrealistic, if not potentially harmful.

BORON

Historical Overview

In the 1870s it was discovered that borax (sodium borate) and boric acid could be used to preserve foods. For about the next 50 years, borates were considered among the best of preservatives for extending the palatability of foods such as fish, meat, cream, and butter. In 1904, however, it was reported that human volunteers consuming over 500 mg of boric acid per day for 50 days displayed disturbed appetite, digestion, and health. After this report, the opinion that boron posed a risk to health gained momentum; by the middle 1950s, boron was essentially banned throughout the world as a food preservative.

In 1923 boron was shown to be essential for plants. About 15 years later, attempts to demonstrate boron essentiality for higher animals began; these attempts were unsuccessful. Thus, before 1980 students of biochemistry and nutrition were taught that boron was a unique element because it was essential for plants but not for higher animals. In 1981, it was reported that boron stimulated growth and partially prevented leg abnormalities present in marginally cholecalciferol-deficient chicks. Since then, evidence has been accumulating indicating that boron has an essential function in higher animals, including humans.

Chemistry

Boron biochemistry is essentially that of boric acid, which exists as $B(OH)_3$ and $B(OH)_4^-$ in dilute solutions at the pH of blood (7.4); because the pK_a of boric acid is 9.2, the abundance of these two species in blood should be 98.4 and 1.6%, respectively.

Boric acid forms ester complexes with hydroxyl groups of organic compounds; this occurs preferentially when the hydroxyl groups are adjacent and *cis*. Boron complexes with many substances of biologic interest, including sugars and polysaccharides, adenosine-5-phosphate, pyridoxine, riboflavin, dehydroascorbic acid, and pyridine nucleotides. To date, five naturally occurring biologic boron esters synthesized by various bacteria have been characterized, the latest being tartrolon B isolated from the myxobacterium *Sorangium cellulosum* (30). All of these boron esters are antibiotics. One of them, boromycin, reportedly can encapsulate alkali metal cations and increase the permeability of the cytoplasmic membrane to potassium ions (31).

Metabolism

Food boron, sodium borate, and boric acid are rapidly absorbed and excreted mostly in the urine. Based on urinary recovery findings, more than 90% of ingested boron is usually absorbed (32, 33). Most ingested boron probably is converted into, and transported through the body as, $B(OH)_3$, the normal hydrolysis end product of most boron compounds and the dominant inorganic species at the pH of the gastrointestinal tract.

Boron is distributed throughout the tissues and organs of animals and humans at concentrations mostly between 4.6 and 55.5 nmol (0.05 and 0.6 μg)/g fresh weight (29, 34). Bone, fingernails, and teeth usually contain several times these concentrations (34).

Evidence that boron is homeostatically controlled includes the rapid urinary excretion of absorbed boron, the lack of accumulation of boron in tissues, and the relatively narrow range of boron concentrations in blood of apparently healthy individuals. For example, mean plasma boron concentrations ranged from 1.85 to 6.2 nmol (20–67 ng) mL in 44 perimenopausal women; upon supplementation with 3.0 mg of boron a day, this range

increased to 2.8 to 6.9 nmol (28–75 ng)/mL (35). In some parts of the world where the daily intake of boron is very high because of environmental exposure (1.6 to 2.5 mmol [17–27 mg]/day), blood boron concentrations have been found to be much higher (41.7–65.9 nmol [450–659 ng]/mL) (36). As with other mineral elements, overcoming homeostatic mechanisms by high boron intakes elevates tissue boron concentrations.

Functions and Mode of Action

A biochemical function for boron has not been elucidated, even for plants for which boron has been known to be essential for 70 years. Its deficiency in plants, as in humans, has multiple effects. Two hypotheses, which accommodate a large and varied response to boron deprivation and the known biochemistry of boron, have recently been advanced for the biochemical function of boron in higher animals. One hypothesis is that boron acts as a metabolic regulator by complexing with a variety of substrate or reactant compounds that have hydroxyl groups in favorable positions (37). Because this complexing usually results in competitive inhibition of enzymes in vitro, the regulation is hypothesized to be mainly negative. The second hypothesis is that boron has a role in cell membrane function or stability such that it influences the response to hormone action, transmembrane signaling, or transmembrane movement of regulatory cations or anions (38). This hypothesis is supported by the findings that boron influences the transport of extracellular calcium and the release of intracellular calcium in rat platelets activated by thrombin (39) and that boron influences redox actions involved in cellular membrane transport in plants (40).

Deficiency Signs

Listing the signs of boron deficiency for animals is difficult because most studies used stressors such as magnesium or cholecalciferol deficiency to enhance the response to deprivation. However, although the nature and severity of the signs varied with the stressor used, many of the findings indicated that boron deprivation impairs calcium metabolism, brain function, and energy metabolism (37, 39). Recent studies also suggest that boron deprivation impairs immune function and exacerbates adjuvant-induced arthritis in rats (41).

Findings involving boron deprivation of humans come mainly from two studies in which men over the age of 45, postmenopausal women, and postmenopausal women on estrogen therapy were fed a low-boron diet (23 μmol/8.37 MJ [0.25 mg/2000 kcal]) for 63 days and then fed the same diet supplemented with 278 μmol (3.0 mg) of boron/day for 49 days (39). The major differences between the two experiments were the intakes of copper and magnesium: in one experiment they were marginal or inadequate; in the other they were adequate. Some effects of boron supplementation after 63 days of boron depletion found in these experiments are summarized in Table 16.1. Boron supplementation after depletion also enhanced the elevation in serum 17β-estradiol and plasma copper caused by estrogen ingestion (42), altered encephalograms to suggest improved behavioral activation (e.g., less drowsiness) and mental alertness, and improved psychomotor skills and the cognitive processes of attention and memory (43).

Toxicology

In a recent symposium (44), boron was described as having low toxicity when administered orally. Toxicity signs in animals generally occur only after dietary boron exceeds 9.25 μmol (100 μg)/g diet. In humans, the signs of acute toxicity include nausea, vomiting, diarrhea, dermatitis, and lethargy (45). In addition, high-boron intake induces riboflavinuria (46). The signs of chronic boron toxicity have been described as including poor appetite, nausea, weight loss, and decreased sexual activity, seminal volume, and sperm count and motility. Two infants who had their pacifiers dipped into a preparation of borax and honey for a period of several weeks exhibited scanty hair, patchy dry erythema, anemia, and seizures (47). The seizures stopped and the other abnormalities were alleviated when use of the borax and honey preparation was discontinued. Recently, it was suggested that an acceptable safe intake of boron could well be 13 mg/day (48).

Dietary Considerations

In the human studies just described, the subjects responded to a boron supplement after consuming a diet

Table 16.1
Responses of Boron-Deprived (23 μmol/8.37 MJ [0.25 mg/2000 kcal] for 63 days) Men over Age 45, Postmenopausal Women and Postmenopausal Women on Estrogen Therapy to a 278 μmol (3 mg) Boron per Day Supplement for 49 Days[a]

Metabolism Affected	Evidence for Effect
Macromineral and electrolyte	Increased serum 25-hydroxycholecalciferol Decreased serum calcitonin[b]
Energy	Decreased serum glucose[b] Increased serum triglycerides[c]
Nitrogen	Decreased blood urea nitrogen Decreased serum creatinine Decreased urinary hydroxyproline excretion
Oxidative	Increased erythrocyte superoxide dismutase Increased serum ceruloplasmin
Erythropoiesis hematopoiesis	Increased blood hemoglobin[c] Increased mean corpuscular hemoglobin[c] Decreased hematocrit[c] Decreased platelet number[c] Decreased red cell number[c]

[a]See review (39) for references to original articles.
[b]Found when dietary copper was marginal and magnesium was inadequate.
[c]Found when dietary copper and magnesium were adequate.

supplying boron at only about 23 μmol/8.37 MJ (0.25 mg/2000 kcal) for 63 days. Thus, humans apparently have a dietary requirement above this. On the bases of both human and animal data, an acceptable safe range of daily mean intakes of boron for adults could well be 0.09 to 1.2 mmol/day (1.0–13 mg/day) (48).

Foods of plant origin, especially noncitrus fruits, leafy vegetables, nuts, pulses, and legumes are rich sources of boron. Wine, cider, and beer are also high in boron. Meat, fish, and dairy products are poor sources of boron (49). Using food analyses included in the U.S. Food and Drug Administration total diet studies, the mean adult male daily intake has been determined to be 141 μmol (1.52 mg)/day (50) or 112 μmol (1.21 mg)/day (49).

Clinical Considerations

Knowledge about boron nutrition, biochemistry, and metabolism is growing, but more is needed before clinical disorders can be attributed to subnormal boron nutrition. Thus, reports such as those suggesting that low boron status may enhance the susceptibility or exacerbate some forms of arthritis (51) must be viewed with caution. Nonetheless, boron clearly is a biologically dynamic ultratrace element in higher animals, including humans. Thus, boron deprivation may have a role in some disorders of uncertain cause (e.g., osteoporosis, arthritis).

FLUORINE (FLUORIDE)

Historical Overview

Fluorine first attracted nutritional attention when its ion form, fluoride, was identified in the 1930s as causing mottled enamel of teeth known as "Colorado brown stain" or other such descriptive terms. It was also noted at this time that fewer dental caries occurred in areas with mottled enamel and subsequently that fluoride intakes could be achieved that resulted in caries reduction without mottling of teeth (52). In 1945, water fluoridation began as a public health measure. In the 1960s, an association was made between high fluoride intakes and reduced incidence of osteoporosis (53). Although the use of pharmacologic amounts of fluoride to prevent bone loss is still being investigated, its usefulness in this regard seems limited. In the early 1970s, scientists suggested that fluoride is necessary for hematopoiesis, fertility, and growth in mice and rats (53), but this suggestion was based on experiments in which animals were not fed optimal diets. It was later concluded that fluoride affected hematopoiesis, fertility, and growth through pharmacologic mechanisms (53), and thus no substantive evidence exists to support essentiality.

Chemistry

The biochemistry of fluoride has been briefly reviewed (53). Fluorine exists as the fluoride ion or as hydrofluoric acid (HF) in body fluids. However, approximately 99% of total body fluorine is found in mineralized tissues as fluorapatite. Fluoride is incorporated into apatite, a basic calcium phosphate mineral with a theoretical formula of $Ca_{10}(PO_4)_6(OH)_2$, by substituting for the OH^- moiety. This substitution occurs because F^- and OH^- have similar ionic radii and share the same charge and primary hydration number.

Metabolism

Several reviews of fluoride metabolism (52–55) indicate that about 75 to 90% of ingested fluoride is absorbed from the gastrointestinal tract. Generally, less than 20% of ingested fluoride is excreted in the feces. Absorption of fluoride is rapid; about 50% of a moderate dose of soluble fluoride is absorbed in 30 minutes, and complete absorption occurs in 90 minutes. The rapidity of absorption verifies that a significant portion of ingested fluoride is absorbed from the stomach; absorption also occurs throughout the small intestine.

Fluoride absorption is generally considered to occur by passive diffusion and to be inversely related to pH; thus, factors that promote gastric acid secretion increase the rate of absorption. The pH dependence of absorption is consistent with the generally accepted view that HF (pK_a = 3.4), and not ionic fluoride, is the form that is absorbed from the stomach. Diffusion as HF in the small intestine because of its high pH is less likely. In the small intestine, the HF concentration would be very low and the gradient small. In contrast, the concentration and gradient of F^- would be high.

Soluble fluorides, such as sodium fluoride, are almost completely absorbed. Less soluble sources, such as bone meal, are relatively poorly absorbed (less than 50%). Aluminum hydroxide, widely used as an antacid, markedly inhibits fluoride absorption.

The rapid absorption of fluoride following oral ingestion leads to a prompt rise in its plasma concentration. Fluoride in plasma exists in ionic form; it is not bound by plasma proteins or by any other constituent of plasma. However, HF, not ionic fluoride, apparently is the form that is in diffusion equilibrium across cell membranes.

Removal of fluoride from the circulation occurs principally through two mechanisms: renal excretion and calcified tissue deposition. Approximately 50% of fluoride absorbed each day is deposited in the calcified tissues (bone and developing teeth) within 24 hours, which results in about 99% of the body burden of fluoride being associated with these tissues. The rate of uptake by bone is affected by the stage of skeletal development. Renal excretion is the major route for removal of fluoride from the body; about 50% of the daily intake is cleared by the kidney. Urinary excretion of fluoride is directly related to urinary pH; thus, factors that affect urinary pH, such as diet, drugs, metabolic or respiratory disorders, and altitude of residence, can affect how much absorbed fluoride is excreted.

Functions and Mode of Action

The major known function of fluoride is its role in protecting against pathologic demineralization of calcified tissues. This is not an essential function in the true sense, but a beneficial action, described elsewhere in this treatise (Chapters 66 and 85). An essential function has not been described for fluoride.

Deficiency Signs

In the early 1970s, it was reported that mice fed low fluoride diets (as low as 0.26 nmol [5 ng]/g) exhibited anemia and infertility, compared with mice supplemented with 2.6 μmol (50 μg) F/mL of drinking water (53). These findings were obtained with diets that were iron deficient, however, and high dietary fluoride (similar to that fed to the supplemented controls) was shown to improve iron absorption or use. Thus, mice fed low-fluoride diets containing sufficient iron exhibited neither anemia nor infertility. Relatively high fluoride supplementation (130–395 nmol [2.5–7.5 μg]/g to a diet containing 2.1 to 24.2 nmol [0.04–0.46 μg]/g) slightly improved the growth of suboptimally growing rats (56) and (1.3 μmol [25 μg]/g diet) enhanced growth in chicks (57). These growth-promoting effects were probably pharmacologic. High or pharmacologic amounts of fluoride have also been found to depress lipid absorption (53) and to alleviate nephrocalcinosis induced by phosphorus feeding (58). Recently, it was reported that a fluoride deficiency in goats decreased life expectancy and caused pathologic histology in the kidney and endocrine organs (59, 60). These findings need to be confirmed in a nonruminant species before being accepted as evidence for essentiality in higher animals. In summary, unequivocal or specific signs of fluoride deficiency have not been described for higher animals including humans. However, fluoride still must be recognized as a trace element with beneficial properties.

Toxicology

The toxicity of fluoride has received much attention since it was discovered to cause mottled teeth. Reviews of fluoride toxicity (52, 53, 55) indicate that chronic toxicity through excessive intake, mainly through water supplies and industrial exposure, has been reported in many parts of the world. Ingestion of water and food containing in excess of 0.1 mmol (2 mg) F/kg results in dental fluorosis or mottled enamel, ranging from barely discernible to stained and pitted enamel. Crippling skeletal fluorosis apparently occurs in people who ingest 0.53 to 1.32 mmol F (10–25 mg) per day for 7 to 20 years (55). The asymptomatic preclinical stage of skeletal fluorosis is characterized by slight increases in bone mass that are detectable radiographically. As skeletal fluorosis progresses, symptoms range from occasional stiffness or pain in the joints to chronic joint pain and osteoporosis of long bones. In severe cases of chronic fluorosis, muscle wasting and neurologic defects occur.

The signs and symptoms of acute fluoride toxicity are nausea, vomiting, diarrhea, abdominal pain, excessive salivation and lacrimation, pulmonary disturbances, cardiac insufficiency and weakness, convulsions, sensory disturbances, paralysis, and coma (55). The probably acute toxic dose or the minimum dose of fluoride that could cause toxic signs and symptoms, including death, is 0.26 mmol (5 mg) per kg body weight (52).

Dietary Considerations

Although fluoride is not generally considered an essential element for humans, it is still considered a beneficial element. The Food and Nutrition Board (2) has established the following ESADDIs for fluoride: infants aged 0 to 0.5 years, 5.3 to 26.3 μmol or 0.1 to 0.5 mg; infants aged 0.5 to 1 years, 10.5 to 52.6 μmol or 0.2 to 1.0 mg; children and adolescents aged 1 to 3 years, 26.3 to 78.9 μmol or 0.5 to 1.5 mg, aged 4 to 6 years, 52.6 to 131.6 μmol or 1.0 to 2.5 mg, aged 7 years and older, 78.9 to 131.6 μmol or 1.5 to 2.5 mg; adults, 78.9 to 210.5 μmol or 1.5 to 4.0 mg. These ESADDIs are based on amounts that protect against dental caries and generally do not result in any mottling of teeth.

The major source of dietary fluoride in the United States is drinking water; about 52% of the population uses water with a fluoride concentration adjusted between 36.8 to 63.2 μmol (0.7–1.2 mg)/L (55). The richest dietary sources of fluoride are tea and marine fish that are consumed with their bones. Fluoride is ubiquitous in foodstuffs, but similar products can vary greatly with source. Thus, estimating fluoride intakes is difficult. For an adult male residing in a community with fluoridated water, estimates of daily fluoride intake range from 52.8 to 157.9 μmol (1–3 mg) per day. This range is reduced to less than 52.8 μmol (1.0 mg) per day in nonfluoridated areas (55). Foods marketed in different parts of the United States contribute only 15.8 to 31.6 μmol (0.3–0.6 mg) to the daily intake of fluoride (2).

Clinical Considerations

At present, the clinical importance of fluoride is not through its nutritional effects but through its beneficial pharmacologic (anticariogenic and possibly antiosteoporotic) or toxicologic (dental and skeletal fluorosis) actions. However, the possibility that fluoride is an essential nutrient should not be dismissed. It seems possible that fluoride could have a role in biologic mineralization.

MANGANESE

Historical Overview

Although manganese was known to be a constituent of animal tissues as early as 1913, it was not until 1931 that manganese deficiency signs were described for experimental animals. Manganese deficiency has since been induced in numerous species of animals. A few cases of

possible manganese deficiency in humans have recently been reported. The importance of manganese in health and disease is the focus of a recent book (61).

Chemistry

A brief review of manganese biochemistry (62) indicated that the characteristic oxidative state of manganese in solution, in metal-enzyme complexes, and in metalloenzymes is Mn^{2+}. Mn^{3+} also is important in vivo; it is the oxidative state in the enzyme manganese superoxide dismutase, the form that binds to transferrin, and probably the form that interacts with Fe^{3+}. Ingested Mn^{2+} is thought to be converted into Mn^{3+} in the duodenum. In manganese-activated biologic reactions, the enzyme-manganese interaction involves either chelation of the metal ion with a phosphate-containing substrate (particularly adenosine triphosphate [ATP]) or a direct interaction with the protein. The chemistry of Mn^{2+} is similar to that of Mg^{2+}. Therefore, for most enzymatic reactions activated by Mn^{2+}, the activation is nonspecific; Mg^{2+} can also act as the activator.

Metabolism

For the adult human, absorption of manganese from the diet has long been assumed to be near 5%. This estimate is complicated, however, by the fact that endogenous manganese is almost totally excreted through biliary, pancreatic, and intestinal secretions into the gut. If manganese status is adequate, endogenous excretion of absorbed manganese into the gut is so rapid that it is difficult to determine the portion of fecal manganese not absorbed from the diet and the portion endogenously excreted. Thus, the true absorption of manganese by humans probably remains to be determined. Absorption efficiency apparently declines as dietary intake of manganese increases (63) and increases with low manganese status (64). On the other hand, endogenous excretion of manganese does not seem to be markedly influenced by dietary intake or status (64). Thus, the often cited hypothesis that manganese homeostasis is regulated mainly by variable excretion through the digestive tract probably needs to be replaced with one that has the control of absorption in the gut as a major factor.

Absorption of manganese, through an unestablished mechanism, apparently occurs equally well throughout the small intestine. Some findings indicate that manganese is absorbed through an active transport mechanism that is a rapidly saturable process involving a high-affinity, low-capacity, active-transport system (65). On the other hand, diffusion has been implicated because studies with brush border membrane vesicles indicated that mucosal transport of manganese occurs through a nonsaturable, simple diffusion process (66). Perhaps both processes are involved in manganese movement across the gut; studies using CACO-2 cells, which mimic many of the actions of enterocytes, showed that apical to basolateral manganese uptake and transport were strictly concentration dependent, but basolateral to apical uptake and transport were saturable (67). Manganese might well be absorbed by a two-step mechanism: initial uptake from the lumen followed by transfer across the mucosal cells. The two kinetic processes operate simultaneously, with manganese competing with iron and cobalt for common binding sites in both processes. Thus, one of these metals, if present in a high amount, can exert an inhibitory effect on absorption of the others.

The form of manganese entering the portal blood from the gastrointestinal tract is also controversial. In addition to hydrated manganese complexes, Mn^{2+} bound both to plasma α_2-macroglobulin (68) and to albumin (64) have been suggested to be the form. Regardless of the form, manganese is removed rapidly from the blood by the liver. A fraction is oxidized to Mn^{3+} and is bound to the plasma transport protein transferrin or possibly to a specific transmanganin protein. Transferrin-bound manganese is taken up by extrahepatic tissue.

Within cells, manganese is found predominantly in mitochondria, and thus organs rich in mitochondria, such as liver, kidney, and pancreas, have relatively high manganese concentrations; in contrast, plasma manganese in humans is extremely low (68).

As indicated above, manganese is almost totally excreted in feces; only trace amounts are found in urine. Excretion of absorbed manganese into the gut is rapid and apparently occurs in two waves. The first wave results from the clearance of initially absorbed manganese; the second represents a combination of initially absorbed manganese and that arising from the enterohepatic circulation.

Functions and Mode of Action

Manganese is known to function in enzyme activation and be a constituent of several metalloenzymes (69). The numerous enzymes that can be activated by manganese include oxidoreductases, lyases, ligases, hydrolases, kinases, decarboxylases, and transferases. Most enzymes activated by manganese can also be activated by other metals, especially magnesium; exceptions are the manganese-specific activation of glycosyltransferases and possibly of xylosyltransferase (62). There are only a few manganese metalloenzymes; these include arginase, pyruvate carboxylase, glutamine synthetase, and manganese superoxide dismutase (62, 69).

Deficiency Signs

Manganese deficiency (reviewed in refs. 70, 71) has been induced in many species of animals. Signs of deficiency include impaired growth, skeletal abnormalities, disturbed or depressed reproductive function, ataxia of the newborn, and defects in lipid and carbohydrate metabolism.

A review of studies reportedly describing manganese

deficiency in humans finds that most are not conclusive. One frequently cited case concerns a man who, after consuming a semipurified formula diet for an extended period, developed weight loss, depressed growth of hair and nails, dermatitis, and hypocholesterolemia. Also, his black hair developed a reddish tinge, and his clotting-protein response to vitamin K supplementation was abnormal. After these symptoms appeared, it was realized that manganese had been left out of his diet. The subject responded to a mixed hospital diet containing manganese (72). Unfortunately, supplementation with manganese alone was not tried. In another study (73), men were fed a purified diet containing only 2.0 μmol (0.11 mg) manganese per day for 39 days. They exhibited decreased serum cholesterol concentrations and a fleeting dermatitis. Calcium, phosphorus, and alkaline phosphatase activity increased in blood. Short-term manganese supplementation (10 days), however, did not reverse these changes. More recently, 14 young women consumed a conventional diet providing 18.2 μmol (1.0 mg) or 101.8 μmol (5.6 mg) manganese per day each for 39 days (74). Low dietary manganese slightly increased plasma glucose concentration during an intravenous glucose tolerance test (IVGTT) and increased menstrual losses of manganese, calcium, iron, and total hemoglobin. These intriguing findings need to be confirmed before they are accepted as signs of manganese deprivation because the subjects did not exhibit negative manganese balance during manganese deprivation, nor were the changes highly significant. Probably the most convincing case of manganese deficiency is that of a child on long-term parenteral nutrition who exhibited diffuse bone demineralization and poor growth that were corrected by manganese supplementation (75).

Manganese deprivation may contribute to disease processes. Low dietary manganese or low blood and tissue manganese has been associated with osteoporosis, diabetes, epilepsy, atherosclerosis, and impaired wound healing (61).

Toxicology

Manganese is often considered to be among the least toxic of the trace elements through oral intake. However, manganese may be of more toxicologic concern than believed in the past, especially for people with compromised homeostatic mechanisms or infants whose homeostatic control of manganese is not fully developed. In the past, the most common form of manganese toxicity identified in humans resulted from chronic inhalation of large amounts of airborne manganese as found in mines, steel mills, and some chemical industries. In these cases of toxicity, the principal organ affected was the brain. In miners intoxicated by manganese, the initial signs of toxicity were severe psychiatric abnormalities including hyperirritability, violent acts, and hallucinations, which were referred to as "manganic madness." As toxicity progressed, a permanent crippling neurologic disorder of the extrapyramidal system resulted that displayed morphologic lesions similar to those associated with Parkinson's disease (76). Although there is no conclusive report of oral toxicity of manganese in humans, many suggestive findings have recently appeared. High brain manganese concentrations have been associated with neurologic dysfunction (77). High manganese concentrations in hair have been associated with violent behavior (78). An RfD (safe daily intake over a lifetime) of 2.6 μmol (0.14 mg) per kg of body weight per day has been determined (79); for a 70-kg man this is a daily intake of 0.18 mmol (9.8 mg).

Dietary Considerations

The current United States ESADDIs for manganese (2) (see Tables of RDI [RDA] in the Appendix) are the following: infants aged 0 to 0.5 years, 5.5 to 10.9 μmol or 0.3 to 0.6 mg, and aged 0.5 to 1 years, 5.5 to 18.2 μmol or 0.6 to 1.0 mg; children and adolescents aged 1 to 3 years, 18.2 to 27.3 μmol or 1.0 to 1.5 mg, aged 4 to 6 years, 27.3 to 36.4 μmol or 1.5 to 2.0 mg, aged 7 to 10 years, 36.4 to 54.6 μmol or 2.0 to 3.0 mg, and aged 11 years and older, 36.4 to 91.0 μmol or 2.0 to 5.0 mg; adults, 36.4 to 91.0 μmol or 2.0 to 5.0 mg. Few data are available to support these estimates.

The above-cited values apparently were set mainly through the reasoning that most dietary intakes fall in this range and do not result in deficiency or toxicity signs. Other evidence used was balance data of questionable value. Thus, the ESADDIs of manganese may need modification as additional data become available. One recent study indicated a minimal requirement for manganese of 13.5 μmol (0.74 mg) per day for young men, based on obligatory losses while consuming a semipurified, manganese-deficient formula diet (73). However, this amount probably did not allow for storage of manganese for use at times of enhanced need nor for the possible inhibition of manganese absorption by dietary substances such as fiber. A requirement near 18 μmol (1.0 mg) per day was indicated in another study in which 14 young women were fed that amount for 39 days without negative manganese balance occurring (74). Five men who received varying amounts of manganese in a diet of conventional foods for 105 days exhibited negative retention of manganese with daily dietary intakes of 22.0, 37.5, and 52.6 μmol (1.21, 2.06, and 2.89 mg), but positive retention was found at daily dietary intakes of 48.2 and 69.0 μmol (2.65 and 3.79 mg). Regression analysis of intake versus balance yielded a recommended daily intake of 63.7 μmol (3.5 mg) (79). This value is difficult to reconcile with the fact that most diets contain less manganese, and no evidence that manganese deficiency is a problem has appeared. Also, attempts to produce manganese deficiency by feeding diets containing as little as 13.5 to 18.2 μmol (0.74 or 1.0 mg) per day resulted in no conclusive or significant effects on the health of adults. These studies show that no firm

data are available to establish the lower value of the ESADDI of manganese.

The upper level of acceptable intake probably should be the amount encountered in a diet high in manganese-rich foods that allows positive balance if the diet contains large quantities of substances that inhibit manganese absorption. Thus, increasing the upper value to 182 μmol (10 mg) per day needs to be considered, especially since an RfD has been set at that level.

Unrefined cereals, nuts, leafy vegetables, and tea are rich in manganese; refined grains, meats, and dairy products contain small amounts (80). Most reported daily mean intakes of manganese throughout the world fall between 9.5 and 196 μmol (0.52 and 10.8 mg) (79).

Clinical Considerations

Determination of the importance of manganese in human nutrition is urgently needed. Key issues are whether or not low manganese status is an important clinical consideration for osteoporosis, atherosclerosis, epilepsy, diabetes, and wound healing and whether or not manganese toxicity is a significant factor in abnormal brain function.

MOLYBDENUM

Historical Overview

Reviews of molybdenum (81, 82) state that evidence for the essentiality of this element first appeared in 1953, when xanthine oxidase was identified as a molybdenum metalloenzyme. However, molybdenum deficiency signs appeared in rats and chickens only when the diet contained massive amounts of tungsten, an antagonist of molybdenum metabolism. These studies showed that the dietary requirement to maintain normal growth of animals was less than 10.4 nmol (1 μg) molybdenum/g diet, an amount substantially lower than requirements for other trace elements recognized essential at the time. Thus, molybdenum was not considered of much practical importance in animal and human nutrition. Consequently, over the past 35 years, relatively little effort has been devoted to studying the metabolic and pathologic consequences of molybdenum deficiency in monogastric animals or humans.

Chemistry

Molybdenum is a transition element that readily changes its oxidation state and can thus act as an electron transfer agent in oxidation-reduction reactions. In the oxidized form of molybdoenzymes, molybdenum is probably present in the 6+ state. Although the enzymes during electron transfer are probably first reduced to the 5+ state, other oxidation states have been found in reduced enzymes. Molybdenum is present at the active site of enzymes as a small nonprotein cofactor containing a pterin nucleus (82). Almost all molybdenum in liver exists as this cofactor, with about 60% of the total amount in sulfite oxidase and xanthine oxidase. In addition to the molybdenum cofactor and "enzymatic" molybdenum, the other important form of molybdenum is the molybdate ion (MoO_4^{2-}) (83), which is the main form in blood and urine.

Metabolism

Molybdenum (except as MoS_2) in foods and in the form of soluble complexes is readily absorbed. Humans absorbed 88 to 93% of the molybdenum fed as ammonium molybdate in a liquid formula component of a diet (84). In another study, about 57% of intrinsically labeled molybdenum in soy and 88% in kale were absorbed (85). Molybdenum absorption occurs rapidly in the stomach and throughout the small intestine, with the rate of absorption being higher in the proximal than in the distal parts (83). Whether an active or a passive mechanism is more important in the absorption of molybdenum is uncertain. One study indicated that at low concentrations, molybdenum absorption is carrier mediated and active (86). Another study showed that in vivo absorption rates were essentially the same over a 10-fold range of molybdenum concentrations, which suggests that molybdate was absorbed by diffusion only (87). Molybdate possibly is moved both by diffusion and by active transport, but at high concentrations, the relative contribution of active transport to molybdenum flux is small.

Molybdate is absorbed and transported loosely attached to erythrocytes in the blood; it tends to bind specifically to α_2-macroglobulin (88). Organs that retain the highest amounts of molybdenum are liver and kidney (81, 83, 88).

After absorption, most molybdenum is turned over rapidly and eliminated as molybdate through the kidney (84); this elimination is increased as dietary intake is increased. Thus, excretion rather than regulated absorption is the major homeostatic mechanism for molybdenum. Nonetheless, significant amounts of this element are excreted in the bile (88).

Functions and Mode of Action

Molybdenum functions as an enzyme cofactor (81, 82). Molybdoenzymes catalyze the hydroxylation of various substrates (89). Aldehyde oxidase oxidizes and detoxifies various pyrimidines, purines, pteridines, and related compounds. Xanthine oxidase/dehydrogenase catalyzes the transformation of hypoxanthine to xanthine and of xanthine to uric acid. Sulfite oxidase catalyzes the transformation of sulfite to sulfate.

Molybdate might also be involved in stabilizing the steroid-binding ability of unoccupied steroid receptors (90, 91). During isolation procedures, molybdate protects steroid hormone receptors, such as the glucocorticoid receptor, against inactivation. It is hypothesized, however, that molybdate affects the glucocorticoid receptor

because it mimics an endogenous compound called "modulator."

Deficiency Signs

The signs of molybdenum deficiency in animals have been reviewed (81). Deficiency signs in goats and minipigs are depressed feed consumption and growth, impaired reproduction characterized by increased mortality in both mothers and offspring, and elevated copper concentrations in liver and brain. A molybdenum-responsive syndrome found in hatching chicks is characterized by a high incidence of late embryonic mortality, mandibular distortion, anophthalmia, and defects in leg bone development and feathering. Skeletal lesions, subsequently detected in older birds, include separation of the proximal epiphysis of the femur, osteolytic changes in the femoral shaft, and lesions in the overlying skin that ultimately were attributed to intense irritation in these areas. The incidence of this syndrome was particularly high in commercial flocks reared on diets containing high concentrations of copper (a molybdenum antagonist) as a growth stimulant. These apparently dissimilar pathologic changes could possibly be explained by a defect in sulfur metabolism.

Recognition that molybdenum is a component of sulfite oxidase whose deficiency disrupts cysteine metabolism has resulted in identification of human disorders caused by a lack of functioning molybdenum. A lethal inborn error in metabolism resulting from a sulfite oxidase deficiency is characterized by severe brain damage; mental retardation; dislocation of ocular lenses; increased urinary output of sulfite, *S*-sulfocysteine, and thiosulfate; and decreased urinary output of sulfate (82). A patient receiving prolonged TPN therapy acquired a syndrome described as "acquired molybdenum deficiency." This syndrome, exacerbated by methionine administration, was characterized by hypermethioninemia, hypouricemia, hyperoxypurinemia, hypouricosuria, and low urinary sulfate excretion. In addition, the patient suffered mental disturbances that progressed to coma. Supplementation with ammonium molybdate improved the clinical condition, reversed the sulfur-handling defect, and normalized uric acid production (92).

Toxicology

Large oral doses are necessary to overcome the homeostatic control of molybdenum (81, 83). Thus, molybdenum is a relatively nontoxic element; in nonruminants, an intake of 1.04 to 52.1 mmol (100–5000 mg)/kg of food or water is required to produce clinical symptoms. Ruminants are more susceptible to elevated amounts of dietary molybdenum. The mechanism of molybdenum toxicity is uncertain. Most toxicity signs are similar or identical to those of copper deficiency (i.e., growth depression and anemia). In humans, both occupational and high dietary exposures to molybdenum have been linked by epidemiologic methods to elevated uric acid concentrations in blood and an increased incidence of gout.

Dietary Considerations

The current United States ESADDIs for molybdenum (2) (see Tables of RDI [RDA] in the Appendix) are the following: infants aged 0 to 0.5 years, 0.16 to 0.31 μmol or 15 to 30 μg, and aged 0.5 to 1.0 years, 0.21 to 0.42 μmol or 20 to 40 μg; children and adolescents aged 1 to 3 years, 0.26 to 0.52 μmol or 25 to 50 μg, aged 4 to 6 years, 0.31 to 0.78 μmol or 30 to 75 μg, aged 7 to 10 years, 0.52 to 1.76 μmol or 50 to 150 μg, and aged 11 years or older, 0.78 to 2.08 μmol or 75 to 200 μg; adults, 0.78 to 2.61 μmol or 75 to 250 μg. Data to support these estimates are scant. These values apparently were set by using balance data (which may be questionable) and the reasoning that usual dietary intakes are within this range without apparent signs of deficiency or toxicity. Recent studies indicate that the requirement for molybdenum in adults is actually close to 0.26 μmol (25 μg) per day (93).

The daily intake of molybdenum ranges between 0.52 and 3.65 μmol (50 and 350 μg) (94–96). Most diets, however, apparently supply about 0.52 to 1.04 μmol (50–100 μg) molybdenum per day. The richest food sources of molybdenum include milk and milk products, dried legumes or pulses, organ meats (liver and kidney), cereals, and baked goods. The poorest sources of molybdenum include nonleguminous vegetables, fruits, sugars, oils, fats, and fish (95, 96).

Clinical Considerations

Except for the molybdenum-responsive patient with "acquired molybdenum deficiency" resulting from long-term use of TPN, there is no indication that molybdenum deficiency is of clinical importance. Nonetheless, the search for possible molybdenum-responsive syndromes in humans is still warranted because situations may be occurring where molybdenum nutriture is important. For example, low dietary molybdenum might be detrimental to human health and well-being through an effect on the detoxification of xenobiotic compounds. The molybdenum hydroxylases apparently are as important as the microsomal monooxygenase system in the metabolism of drugs and foreign compounds (89). This may be why molybdenum has an inhibitory effect on some forms of cancer in animal models (97).

NICKEL

Historical Overview

An earlier review of nickel (98) stated that although nickel was first suggested to be nutritionally essential in 1936, strong evidence for essentiality did not appear until 1970. Studies between 1970 and 1975, however, gave inconsistent signs of nickel deprivation, probably because of suboptimal experimental conditions. Since 1975, diets and environments that allow optimal growth and survival of laboratory animals have been used in studies of nickel nutrition and metabolism. Thus, most of the significant

biochemical, nutritional, and physiologic studies of nickel appeared after 1975.

Chemistry

Books devoted to nickel have extensive reviews of the biochemistry of this element (99, 100). These reviews indicate that monovalent, divalent, and trivalent forms of nickel apparently are important in biochemistry. Like other ions of the first transition series, Ni^{2+} can complex, chelate, or bind with many substances of biologic interest. This binding, particularly by amino acids (especially histidine and cysteine), proteins (especially albumin), and by a macroglobulin called nickeloplasmin, probably is important in the extracellular transport, intracellular binding, and urinary and biliary excretion of nickel. Ni^{2+} in a tightly bound form is required for the activity of urease, an enzyme found in plants and microorganisms. In the microbial enzyme, methyl coenzyme M reductase, nickel is present in a chromophore called factor F430, which is a tetrapyrrole similar in structure to that in vitamin B_{12}. Ni^{3+} apparently is essential for enzymatic hydrogenation, desulfurization, and carboxylation reactions in mostly anaerobic microorganisms. In some of these reactions, the redox action of nickel may involve the 1+ oxidation state, especially in that of methyl coenzyme M reductase. Nickel is also a structural component of some enzymes.

Metabolism

When nickel in water is ingested after an overnight fast or in low quantities, as much as 50%, but usually closer to 20 to 25%, of the dose is absorbed (101, 102). Certain foodstuffs and simple substances, including milk, coffee, tea, orange juice, and ascorbic acid, however, depress this high absorption (101). Foods such as those found in a typical Guatemalan meal or in a North American breakfast suppress absorption of nickel to less than 1%. Thus, nickel is often poorly absorbed (less than 10%) when ingested with typical diets. Nickel absorption is enhanced by iron deficiency, pregnancy, and lactation (103, 104).

The mechanisms involved in transport of nickel through the gut are not conclusively established. Persuasive evidence indicates that no specific nickel carrier mechanism exists at the brush border membrane (104); this means that absorption probably depends on the efficiency of mucosal trapping via charge neutralization on the membrane. In other words, nickel crosses the basolateral membrane via passive leakage or diffusion, perhaps as an amino acid complex or some other low-molecular-weight complex. Passage as a lipophilic complex is a possibility, because these types of complexes markedly increase the nickel concentrations in tissues of experimental animals (106). However, there is also some evidence for energy-driven transport of nickel across the mucosal epithelium (104, 107).

Nickel transported in blood is principally bound to serum albumin (108). Small amounts of nickel in serum are associated with the amino acid L-histidine and with α_2-macroglobulin (108, 109). No tissue or organ significantly accumulates orally administered physiologic doses of nickel. In humans, the thyroid and adrenal glands apparently have relatively high nickel concentrations, with reported values of 2.40 and 2.25 μmol (141 and 132 μg)/kg dry weight, respectively (110). Most organs contain less than 0.85 μmol (50 μg) nickel/kg dry weight.

Although fecal nickel excretion (mostly unabsorbed nickel) is 10 to 100 times as great as urinary excretion, most of the small fraction of nickel absorbed is rapidly and efficiently excreted through the kidney as urinary low-molecular-weight complexes. Measurable amounts of nickel are also lost in sweat and bile. The nickel content in sweat is high (about 1.19 μmol or 70 μg/L), which points to active nickel secretion by the sweat glands (111). Biliary loss of nickel has been estimated at 34 to 85 nmol (2–5 μg) per day (110).

Functions and Mode of Action

No biochemical function for nickel has been clearly defined for higher animals or humans. Nickel may, however, function as a cofactor or structural component in specific metalloenzymes in higher organisms, because such enzymes have been identified in bacteria, fungi, plants, and invertebrates. These nickel-containing enzymes include urease, hydrogenase, methyl coenzyme M reductase, and carbon monoxide dehydrogenase (99, 100). Nickel may have a function in higher animals that involves a pathway using vitamin B_{12} and/or folic acid. Both these vitamins affect signs of nickel deprivation in rats (112, 114). The interaction between nickel and folic acid affects the vitamin B_{12}– and folic acid–dependent pathway of methionine synthesis from homocysteine (114). Nickel might also have a very basic function, because nickel in vitro is a calcium channel blocker (115) and can activate the Ca^{2+} "receptor" on the osteoclast to elicit cytosolic Ca^{2+} signals (116).

Deficiency Signs

Signs of nickel deficiency have not been described for humans. The reported signs of nickel deprivation for six animal species—chick, cow, goat, pig, rat, and sheep—are extensive and have been listed in several reviews (98, 103, 117). Unfortunately, many of the reported signs may have been misinterpreted manifestations of pharmacologic actions of nickel (118). High dietary nickel, used in some experiments, may have alleviated an abnormality caused by something other than a nutritional deficiency of nickel (many diets were apparently low in iron). However, recent studies with rats and goats indicate that nickel deprivation depresses growth, reproductive performance, and plasma glucose and alters the distribution of other elements in the body, including calcium, iron, and zinc. As with other ultratrace elements, the nature and severity of signs of nickel deprivation are affected by diet composition. For

example, both vitamin B_{12} and folic acid affect the response to nickel deprivation (112–114).

Toxicology

Life-threatening toxicity of nickel through oral intake is unlikely. Because of excellent homeostatic regulation, nickel salts exert their toxic action mainly by gastrointestinal irritation and not by inherent toxicity (117). Generally, concentrations of Ni above 4.26 μmol (250 μg)/g of diet are required to produce signs of nickel toxicity (such as depressed growth and anemia) in animals; by weight extrapolation, a daily oral dose of 4.26 mmol (250 mg) of soluble nickel should produce toxic symptoms in humans. However, more moderate doses of nickel may have adverse effects in humans. An oral dose in water as low as 10.2 μmol (0.6 mg) nickel as nickel sulfate, which is well absorbed, given to fasting subjects produced a positive skin reaction in some individuals with nickel allergy (119). That dose is only a few times higher than the human daily requirement postulated on the basis of results from animal studies.

Dietary Considerations

Because of the strong circumstantial evidence indicating that nickel is essential for several animals, a reasonable hypothesis is that nickel is required by humans also. Moreover, knowledge about the nickel requirements of animals is helpful in estimating the amount of nickel possibly required by humans. Most monogastric animals have an apparent nickel requirement of less than 3.41 μmol (200 μg)/kg diet. On the basis that adult humans usually consume 500 g of a mixed diet daily (dry basis), a dietary requirement for humans of 426 to 596 nmol (25–35 μg) per day has been suggested (120). Total dietary nickel intakes of humans vary greatly with the amounts and proportions of foods of animal (nickel-low) and plant (nickel-high) origin consumed. Rich sources of nickel include chocolate, nuts, dried beans, peas, and grains (95, 120, 121); diets high in these foods could supply more than 15.33 μmol (900 μg) nickel per day. Conventional diets, however, often provide less than 2.55 μmol (150 μg) daily (some much less than 1.70 μmol [100 μg] daily). Examples of reported intakes are 1.18 to 2.76 μmol (69–162 μg) per day in the United States (95) and 2.21 μmol (130 μg) per day (range of 1.02–4.43 μmol or 60–260 μg) in Denmark (121).

Clinical Considerations

Until more is known about the physiologic function of nickel and its dietary requirement, it is inappropriate to suggest specific disorders other than nickel dermatitis as wholly or partially attributable to abnormal nickel nutrition. However, be aware that nickel status affects the functions of vitamin B_{12} and folic acid, two nutrients receiving increasing clinical attention.

SILICON

Historical Overview

As early as 1911, researchers (122) suggested that silicon might have an antiatheroma action. A review of silicon in nutrition (123) indicated that until 1972, silicon was generally considered nonessential, except for some lower classes of organisms (diatoms, radiolarians, and sponges), in which silica serves a structural role. Most of the limited studies on the biochemical, nutritional, and physiologic roles of silicon have been published since 1974.

Chemistry

The chemistry of silicon is similar to that of carbon, its sister element (124). Silicon forms silicon-silicon, silicon-hydrogen, silicon-oxygen, silicon-nitrogen, and silicon-carbon bonds. Thus, organosilicon compounds are analogues of organocarbon compounds. However, substitution of silicon for carbon, or vice versa, in organocompounds results in molecules with different properties, because silicon is larger and less electronegative than carbon.

In animals, silicon is found both free and bound. Silicic acid probably is the free form. The bound form has never been rigorously identified. Silicon might be present in biologic material as a silanolate, an ether (or esterlike) derivative of silicic acid. Bridges of R_1-O-Si-O-R_2 or R_1-O-Si-O-Si-O-R_2 possibly play a role in the structural organization of some mucopolysaccharides or collagen.

Metabolism

Little is known about the metabolism of silicon. Increasing silicon intake increases urinary silicon output up to fairly well defined limits in humans, rats, and guinea pigs. The upper limits of urinary silicon excretion, however, apparently are not set by the excretory ability of the kidney, because urinary excretion can be elevated above these upper limits by peritoneal injection of silicon (125). Thus, the upper limits apparently are set by the rate and extent of silicon absorption from the gastrointestinal tract. The form of dietary silicon determines whether it is well absorbed. In one study, humans absorbed only about 1% of a large single dose of an aluminosilicate compound but absorbed more than 70% of a single dose of methylsilanetriol salicylate, a drug used in the treatment of circulatory ischemias and osteoporosis (126). Some dietary forms of silicon must be well absorbed, because daily urinary silicon excretion in humans can be a high percentage (close to 50%) of daily silicon intake (127). The mechanisms involved in intestinal absorption and blood transport of silicon are unknown.

Silicon is not protein bound in plasma, where it is believed to exist almost entirely in the undissociated monomeric silicic acid form, $Si(OH)_4$ (123–128). Connective tissues, including aorta, trachea, tendon, bone, and skin and its appendages contain much of the sil-

icon that is retained in the body (123). Absorbed silicon is mainly eliminated via the urine, where it probably exists as magnesium orthosilicate (123, 128).

Functions and Mode of Action

The distribution of silicon in the body and the biochemical changes in bone caused by silicon deficiency indicate that silicon influences bone formation by affecting cartilage composition and ultimately cartilage calcification. In bone (123, 129, 130), silicon is localized in the active growth areas or osteoid layer and within the osteoblasts. In bone of silicon-deficient animals, hexosamine (glycosaminoglycans) and collagen concentrations are depressed, but macromineral composition is not markedly affected. Silicon apparently affects collagen formation, because it is required for maximal bone prolylhydroxylase activity (130), and silicon deficiency decreases ornithine aminotransferase (131); both enzymes are involved in collagen formation. Silicon also apparently is involved with phosphorus in the organic phase in the series of events leading to calcification (129). Thus, silicon possibly has a function that facilitates association between phosphoprotein-mucopolysaccharide macromolecules and collagen, which plays a role in the initiation of calcification and the regulation of crystal growth. The finding that silicon affects gene expression in some diatoms suggests that a similar role might also exist in higher animals (132).

Deficiency Signs

Silicon deficiency signs have not been defined for humans. Most of the signs of silicon deficiency in chickens and rats indicate aberrant metabolism of connective tissue and bone (123, 129, 130, 133). Chicks fed a semisynthetic, silicon-deficient diet exhibit structural abnormalities of the skull and long-bone abnormalities characterized by small, poorly formed joints, defective endochondral growth and depressed contents of articular cartilage, water, hexosamine, and collagen. Silicon deprivation can affect the response to other dietary manipulations. Rats fed a diet low in calcium and silicon and high in aluminum accumulated high amounts of aluminum in the brain; silicon supplements prevented the accumulation (134). Also, high dietary aluminum intakes depressed brain zinc concentrations in thyroidectomized rats fed low dietary silicon; silicon supplements prevented the depression (135). The effects of silicon and aluminum were not seen in nonthyroidectomized rats.

Toxicology

Silicon is essentially nontoxic when taken orally. Magnesium trisilicate, an over-the-counter antacid, has been used by humans for more than 40 years without obvious deleterious effects. Other silicates are food additives used as anticaking or antifoaming agents. However, ruminants consuming plants with a high silicon content may develop siliceous renal calculi. Renal calculi in humans may also contain silicates (123).

Dietary Considerations

Postulating a silicon requirement is difficult because only limited data are available. Rats fed about 0.16 mmol (4.5 mg) silicon/kg diet, mostly as the very available sodium metasilicate, do not differ from rats fed about 1.25 mmol (35 mg) silicon/kg diet; both prevent, equally well, silicon deficiency signs exhibited by rats fed about 36 μmol (1.0 mg) silicon/kg diet (133). Thus, if dietary silicon is highly available, as animal data suggest, the human requirement for silicon is quite small, perhaps in the range of 0.07 to 0.18 mmol (2–5 mg) per day. However, much of the silicon found in most diets probably is not absorbable or as available as sodium metasilicate; significant amounts probably occur as aluminosilicates and silica, from which silicon is not readily available. Thus, the recommended intake of silicon probably should be higher than the estimated requirement. On the basis of balance data, a silicon intake of 1.07 to 1.25 mmol (30–35 mg) per day was suggested for athletes, which was 0.18 to 0.36 mmol (5–10 mg) higher than that for nonatheletes (136).

Total dietary silicon intake of humans varies greatly with the amount and proportions of foods of animal (silicon-low) and plant (silicon-high) origin consumed and with the amounts of refined and processed foods in the diet (137, 138). Normally, refining reduces the silicon content of foods. However, in recent years, silicate additives have been used increasingly as anticaking or antifoaming agents in prepared foods and confections. Although this increases total dietary silicon, most of it is not bioavailable. The silicon content of drinking water and beverages made thereof shows geographic variation; silicon is high in hard-water and low in soft-water areas. The richest sources of silicon are unrefined grains of high fiber content and cereal products (137, 138).

Average daily intakes of silicon apparently range from about 0.71 to 1.79 mmol (20–50 mg) per day. The calculated silicon content of the FDA total diet was 0.68 mmol (19 mg) per day for women and 1.42 mmol (40 mg) for men (138). A human balance study indicated that oral intake of silicon could be about 0.75 to 1.64 mmol (21–46 mg) per day (127). The average British diet has been estimated to supply 1.10 mmol (31 mg) silicon per day (137).

Clinical Considerations

Ample circumstantial evidence indicates that silicon is an essential nutrient for higher animals, including humans. However, more work is needed to clarify the consequences of silicon deprivation in humans. A severe lack of dietary silicon could have detrimental effects on brain and bone function and composition.

VANADIUM

Historical Overview

Findings reported between 1971 and 1974 by four different research groups led many to conclude that vanadium is an essential nutrient. However, many of these findings may have been the consequence of high vanadium supplements (10 to 100 times the amount normally found in natural diets) that induced pharmacologic changes in animals fed imbalanced diets (118, 139, 140). A surge of interest in vanadium started in 1977 when it was rediscovered that vanadate inhibits ATPases (141) and has been maintained by the finding that vanadium is an insulin-mimetic agent (142). The first vanadium-containing enzyme, a bromoperoxidase from a marine alga, was isolated in 1984 (143). These findings have stimulated speculation about the nutritional importance of vanadium, for which the most substantive evidence has appeared only since 1987.

Chemistry

The chemistry of vanadium is complex because the element can exist in at least six oxidation states and can form polymers. In higher animals, the tetravalent and pentavalent states apparently are the most important forms of vanadium (144). The tetravalent vanadyl cation, VO^{2+}, behaves like a simple divalent aquo ion and competes well with Ca^{2+}, Mn^{2+}, Fe^{2+}, etc., for ligand-binding sites. Thus, VO^{2+} easily forms complexes with proteins, especially those associated with iron, such as transferrin and hemoglobin, which stabilize the vanadyl ion against oxidation. The pentavalent form of vanadium is known as vanadate ($H_2VO_4^-$ or more simply VO^{3-}). Vanadate forms complexes, including those that result in its being a phosphate transition-state analogue, and thus competes with or replaces phosphate in many biochemical processes. Vanadate is easily reduced nonenzymatically by relatively small molecules such as ascorbate and glutathione.

Another form of vanadium, the peroxo form, might be responsible for many biologic actions of vanadium, including its insulin-mimetic action and haloperoxidase role (145). Vanadate can interact with O^- formed by NADPH oxidase to generate the peroxovanadyl (V-OO) radical. Peroxovanadyl can in turn remove a hydrogen atom from NADPH to yield vanadyl hydroperoxide (V-OOH). Peroxo (heteroligand) vanadate adducts represent a useful model for the active-site vanadium involved in bromide oxidation in haloperoxidases (145).

Metabolism

Recent reviews of vanadium metabolism (140, 146) found that most ingested vanadium is unabsorbed and is excreted in the feces. Based on the very low concentrations of vanadium normally found in urine compared with the estimated daily intake and fecal content of vanadium, less than 5% of vanadium ingested is absorbed. Animal studies generally support the concept that vanadium is poorly absorbed. However, two studies with rats indicated that vanadium absorption can exceed 10% under some conditions, which suggests caution in assuming that ingested vanadium always is poorly absorbed from the gastrointestinal tract.

Most ingested vanadium is probably transformed in the stomach to VO^{2+} and remains in this form as it passes into the duodenum (147). However, in vitro studies suggest that vanadate can enter cells through phosphate- or other anion-transport systems. This may explain why VO_3^- is absorbed 3 to 5 times more effectively than VO^{2+}. Thus, apparently the different absorbability rates, the effect of other dietary components on the forms of vanadium in the stomach, and the rate at which it is transformed into VO^{2+} markedly affect the percentage of ingested vanadium absorbed (147). Supporting this concept are the reviewed findings showing that a number of substances can ameliorate vanadium toxicity, including EDTA, chromium, protein, ferrous ion, chloride, and aluminum hydroxide (140).

If vanadate appears in the blood, it is quickly converted into the vanadyl cation, most likely in erythrocytes. The vanadyl cation, either absorbed as such or formed in vivo, complexes with transferrin and ferritin in plasma and body fluids (148). It remains to be determined whether vanadyl-transferrin can transfer vanadium into cells through the transferrin receptor or whether ferritin is a storage vehicle for vanadium. Vanadium is rapidly removed from the blood plasma and is retained in highest amounts in the kidney, liver, testes, bone, and spleen. However, little of the absorbed vanadium is retained under normal conditions in the body; most tissues contain less than 196 pmol (10 ng) V/g fresh weight (140). Bone apparently is a major sink for excessive retained vanadium.

Excretion patterns after parenteral administration indicate that urine is the major excretory route for absorbed vanadium (148, 149). However, a significant portion of absorbed vanadium may be excreted through the bile. Human bile contains measurable vanadium (about 20 pmol [1.0 ng]/g) (150), and about 10% of an injected dose of ^{48}V was found in the feces of rats (149).

Both high- and low-molecular-weight complexes of vanadium have been found in urine (148, 149); one of these may be the vanadyl-transferrin complex. The form of vanadium in bile has not been determined.

Functions and Mode of Action

A defined biochemical function for vanadium in higher animals and thus for humans has not been described. Numerous biochemical and physiologic functions for vanadium have been suggested on the basis of its in vitro and pharmacologic actions; these have been reviewed (144, 151, 152) and are too extensive to discuss in detail here. Briefly, in vitro studies with cells and pharmacologic studies with animals have shown that vanadium has

insulin-mimetic properties; numerous stimulatory effects on cell proliferation and differentiation; effects on cell phosphorylation-dephosphorylation; inhibitory effects on the motility of sperm, cilia, and chromosomes; effects on glucose and ion transport across plasma membranes; interfering effects on intracellular ionized calcium movement; and effects on oxidation-reduction processes. Vanadium inhibits numerous ATPases, phosphatases, and phosphoryl transfer enzymes in in vitro cell-free systems. The pharmacologic action of vanadium receiving the most attention recently is its ability to mimic insulin (142).

Enzymatic roles for vanadium have been defined for some algae, lichens, fungi, and bacteria (143, 145, 153). Vanadium enzymes include nitrogenase in bacteria, which reduces nitrogen gas to ammonia, and bromoperoxidase, iodoperoxidase and chloroperoxidase in algae, lichens, and fungi, respectively. The haloperoxidases catalyze the oxidation of halide ions by hydrogen peroxide, thus facilitating the formation of a carbon-halogen bond. The best known haloperoxidase in animals is thyroid peroxidase. Vanadium deprivation in rats affects the response of thyroid peroxidase to changing dietary iodine concentrations (154).

Deficiency Signs

Most of the early reported deficiency signs for vanadium are questionable. The diets used in early vanadium deprivation studies had widely varying contents of protein, sulfur amino acids, ascorbic acid, iron, copper, and perhaps other nutrients that affect, or can be affected by, vanadium (139). Also, vanadium supplemention in these experiments was relatively high compared with apparent need. As a result, it is difficult to determine whether the deficiency signs in early experiments were true deficiency signs, indirect changes caused by an enhanced need for vanadium in some metabolic function, or manifestations of a pharmacologic action of vanadium. Vanadium deficiency signs for humans have not been described.

The uncertainty about vanadium deficiency signs prompted new efforts to characterize a consistent set for animals. In these studies, goats fed diets apparently containing adequate and balanced amounts of all known nutrients exhibited an elevated abortion rate and depressed milk production when deprived of vanadium. About 40% of kids from vanadium-deprived goats died between days 7 and 91 of life, with some deaths preceded by convulsions; only 8% of kids from vanadium-supplemented goats died during the same time. Also, skeletal deformations were seen in the forelegs, and forefoot tarsal joints were thickened (155). In a rat study, vanadium deprivation increased thyroid weight and the thyroid weight:body weight ratio and decreased growth (154). Stressors that change thyroid status or iodine metabolism enhanced the response of rats to vanadium deprivation.

Toxicology

Vanadium is a relatively toxic element. Acute toxicity studies indicate that vanadium is a neurotoxic and hemorrhagic-endotheliotoxic poison with nephrotoxic, hepatotoxic, and probably leukocytotactic and hematotoxic components (156). Apparently, this breadth of toxic effects is the reason for the large number of signs of vanadium toxicity described for animals that vary among species and with dosage (157). Some of the more consistent signs include depressed growth, elevated organ vanadium, diarrhea, depressed food intake, and death. Animal data indicate that long-term daily intake above 196 μmol (10 mg) vanadium might lead to toxicologic consequences. Limited studies with humans support this contention. When 12 subjects were given 265 μmol (13.5 mg) vanadium daily for 2 weeks and then 442 μmol (22.5 mg) vanadium daily for 5 months, five patients exhibited gastrointestinal disturbances and five patients exhibited green tongue (158). In another study, six subjects were fed 88 to 353 μmol (4.5–18 mg) vanadium daily for 6 to 10 weeks; green tongue, cramps, and diarrhea were observed at the higher doses (159).

Dietary Considerations

If vanadium is essential for humans, its requirement most likely is small. The diets used in animal deprivation studies contained only 39 to 491 pmol (2–25 ng) V/g diet; these amounts often did not markedly affect the animals. Vanadium deficiency has not been identified in humans, yet diets generally supply less than 589 nmol (30 μg) vanadium daily and most supply only 294 nmol (15 μg) daily (95, 96, 150). Thus, a daily dietary intake of 196 nmol (10 μg) vanadium probably will meet any postulated requirement. Foods rich in vanadium include shellfish, mushrooms, parsley, dill seed, black pepper, and some prepared foods (150, 161, 162). Beverages, fats and oils, and fresh fruits and vegetables contain the least vanadium (less than 20 to 98 pmol [1–5 ng]/g).

Clinical Considerations

The clinical importance of vanadium is uncertain. It will be necessary to disentangle pharmacologic from nutritional observations to assess the nutritional importance of vanadium and to determine its safe and adequate intakes. Because vanadium is so pharmacologically active, a beneficial clinical role for this element may be found.

OTHER ULTRATRACE ELEMENTS

As indicated above, the evidence for essentiality of aluminum, bromine, cadmium, germanium, lead, lithium, rubidium, and tin is quite limited. Nonetheless, because beneficial claims for the elements are sometimes made in health magazines, newsletters, books, special publications, announcements, and advertisements, they should be considered here. Most likely none of these mineral elements

are of nutritional or toxicologic concern if intakes are near those in a typical well-balanced diet.

Aluminum

A dietary deficiency of aluminum in goats reportedly results in increased abortions, depressed growth, incoordination and weakness in hind legs, and decreased life expectancy (163). Aluminum deficiency has been reported to depress growth in chicks (164). Aluminum toxicity is not a concern for healthy individuals. Cooking foods in aluminum cookware does not lead to toxic intakes of aluminum. Ingestion of high dietary amounts of aluminum is no longer believed to cause Alzheimer's disease. However, high intakes of aluminum from such sources as buffered analgesics and antacids by susceptible individuals (e.g., those with impaired kidney function, including the elderly and low-birth-weight infants) may lead to pathologic consequences and thus should be avoided. Aluminum toxicity is of most concern when contaminated solutions are used for parenteral feeding or for kidney dialysis (165). Aluminum toxicity caused in this manner results in neurotoxicity and adverse skeletal changes. Severe neurotoxicity, called dialysis dementia, is characterized by speech disturbances, disorientation, seizures, and hallucinations. Aluminum skeletal toxicity is characterized by bone pain and fractures. The typical daily dietary intake of aluminum is 74 to 371 μmol (2–10 mg). Rich sources of aluminum include baked goods prepared with chemical leavening agents (e.g., baking powder), processed cheese, grains, vegetables, herbs, and tea (166).

Bromine (Bromide)

It has been reported that a dietary deficiency of the bromide anion results in depressed growth, fertility, hematocrit, hemoglobin, and life expectancy, and in increased milk fat and abortions in goats (167). Also, insomnia exhibited by some hemodialysis patients has been associated with bromide deficiency (168). The bromide anion has a low order of toxicity; thus, it is not of toxicologic concern in nutrition. The typical daily intake of bromide ion is 25 to 100 μmol (2–8 mg). Rich sources of bromide are grains, nuts, and fish (169).

Cadmium

Cadmium deficiency reportedly depresses growth of rats (170) and goats (171). Although cadmium might be an essential element at very low intakes, it is of more concern because of its toxicologic properties (172). Cadmium is a potent antagonist of several essential minerals, including zinc, copper, iron, and calcium. Cadmium has a long half-life in the body and thus high intakes can lead to accumulation resulting in damage to some organs, especially the kidney. The typical daily dietary intake of cadmium is 89 to 178 nmol (10–20 μg). Rich sources of cadmium include shellfish, grains (especially those grown on high-cadmium soils), and leafy vegetables (172).

Germanium

A low germanium intake alters the mineral composition of bone and liver and decreases tibial DNA in the rat (173). Germanium is also touted as having anticancer properties because some organic complexes of this element inhibit tumor formation in animal models (174). High intakes of inorganic germanium, which is more toxic than organic forms of germanium, causes kidney damage (174). Some individuals consuming high amounts of organic germanium supplements contaminated with inorganic germanium have died from kidney failure. The typical daily dietary intake of germanium is 5.5 to 20.7 μmol (0.4–1.5 mg). Rich sources of germanium include wheat bran, vegetables, and leguminous seeds (169).

Lead

A large number of findings from one research group (175, 176) suggest that low dietary intake of lead has adverse effects in pigs and rats. Apparent deficiency signs found include depressed growth; anemia; elevated serum cholesterol, phospholipids, and bile acids; disturbed iron metabolism; decreased liver glucose, triglycerides, LDL-cholesterol and phospholipid concentrations; increased liver cholesterol; and altered blood and liver enzymes. Although lead might have beneficial effects at low intakes, lead toxicity is of more concern than lead deficiency. Lead is considered a major environmental pollutant because of past use of lead-based paints and the combustion of fuels containing lead additives. Lead toxicity (177) results in anemia, kidney damage, and central nervous system abnormalities ranging from ataxia and stupor to coma and convulsions. Ingestion of high amounts of lead from the environment by children has been associated with reduced intelligence and impaired motor function. The typical daily dietary intake of lead is 72 to 483 nmol (15–100 μg). Rich sources of lead include seafood and plant foodstuffs grown under high lead conditions (178).

Lithium

Lithium deficiency reportedly results in depressed fertility, birth weight, and life span and in altered activity of several liver and blood enzymes in goats (179). In rats, lithium deficiency apparently depresses fertility, birth weight, litter size, and weaning weight (180, 181). Lithium is best known for its pharmacologic antimanic properties (182). Its ability to affect mental function perhaps explains the report that incidence of violent crimes is higher in areas with low-lithium drinking water (183). The principal disadvantage in the use of lithium for psychiatric disorders is the narrow safety margin between therapeutic and toxic doses. Mild lithium toxicity results in gastrointestinal disturbances, muscular weakness, tremor, drowsiness, and a dazed feeling (182). Severe toxicity results in coma, muscle tremor, convulsions, and even death (182). The typical daily dietary intake of lithium is 28.8 to 86.5

μmol (200–600 μg). Rich sources of lithium include eggs, processed meat, fish, milk, milk products, potatoes, and vegetables (179).

Rubidium

Rubidium deficiency in goats reportedly results in depressed food intake, growth, and life expectancy and increased spontaneous abortion (184). Rubidium is relatively nontoxic and thus not of toxicologic concern. The typical daily dietary intake of rubidium is 12 to 59 μmol (1–5 mg). Rich sources of rubidium include coffee, black tea, fruits, vegetables (especially asparagus), and poultry (185).

Tin

A dietary deficiency of tin has been reported to depress growth, response to sound, and feed efficiency; to alter the mineral composition of several organs; and to cause hair loss in rats (186, 187). Inorganic tin is relatively nontoxic. However, routine consumption of foods packed in unlacquered tin-plated cans may result in excessive exposure to tin, which could adversely affect the metabolism of other essential trace elements including zinc and copper (188). The typical daily dietary intake of tin is 8 to 337 μmol (1–40 mg). A rich source of tin is canned foods (188).

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